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A ROUTE TO ALDEHYDES AND KETONES BY A FOUR-ELECTRON DECARBOXYLATIVE OXIDATION UTILIZING PYRIDINE N-OXIDE

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One-electron (Kolbe reaction) and two-electron decarboxylative oxidations are well known reactions which have been of great mechanistic and synthetic interest. We now wish to report the discovery of a four-electron decarboxylative oxidation and to suggest a probable reaction path which involves the novel and potentially useful mechanistic concept of functionalization of the the α-position of a carboxylic acid by nucleophilic rather than electrophilic attack.

$$C_6H_5CH_2CO_2H + 2C_5H_5NO + Ac_2O \rightarrow C_6H_5CHO + 2C_5H_5N + CO_2 + 2AcOH$$

The reaction, which is shown for the case of phenylacetic acid, can be performed either on the anhydride or on a mixture of the corresponding acid with acetic anhydride. The oxidizing agent is pyridine N-oxide, two moles of which are consumed per mole of aldehyde or ketone formed. The yields in the oxidation of several acids in the refluxing solvents indicated (for 10-48 hrs.) are listed in the table. Carbon dioxide and pyridine are also formed. In the case of phenylacetic acid, a small quantity of diphenylmaleic anhydride (DPMA) is produced. Isobutyric and butric anhydrides fail to react at an appreciable rate in benzene and toluene, respectively. Very little carbon dioxide is produced under similar conditions from acetic anhydride (xylene), cyclohexanecarboxylic acid (toluene), cyclohexanedicarboxylic and glutaric anhydrides (diethyl Carbitol, b.p. 195°), and trimethylacetic anhydride (xylene).

TABLE I

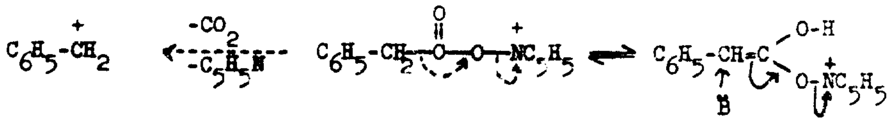
Reactions of Anhydrides and Acids with Pyridine N-Oxide

Run	Anhydride or acid[a]	Solvent	Products (% Yield)
1	Phenylacetic anh.	Benzene	Benzaldehyde (69)
2	Phenylacetic acid[b]	Benzene	Benzaldehyde (68)
3	Diphenylacetic anh.	Benzene	Benzophenone (68)
4	Diphenylacetic acid[b]	Benzene	Benzophenone (62)
5	Isobutyric anh.	Toluene	Acetone (39)
6	Butyric anh.	Xylene	Propionaldehyde[c] (12.4)
7	Acetic anh.	Xylene	2-Acetoxypyridine (d)

[a] Four moles of pyridine N-oxide per mole of anhydride or acid was used. [b] Acetic anhydride (1.5 moles per mole of acid) was employed. [c] Infrared examination revealed the presence of an undetermined quantity of 2-pyridone. [d] Not determined.

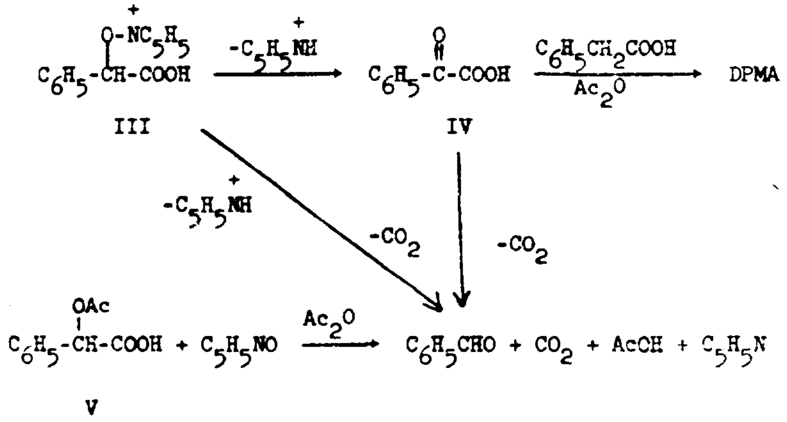
The reactivity sequence indicated in the table could be interpreted as favoring a carbonium ion cleavage reaction of the initially formed N-acyloxypyridinium ion, I, (dotted arrows)(1) followed by oxidation of the carbonium ion by pyridine N-oxide (2). However, militating against such a mechanism are the findings (a) that acetone could not be detected (v.p.c.) in run 6, (b) that benzyl phenylacetate was not produced (v.p.c.) in run 1, (3) and (c) that propene could not be detected in runs 5 and 6. The latter finding also argues against a radical fragmentation of I as does the absence in the product of the phenylacetic acid run of toluene and of 1,2-diphenylethane, the coupling product of benzyl radicals (5).

A reasonable reaction scheme is illustrated for the case of phenylacetic acid. It involves nucleophilic attack of the amine oxide or an acylate anion on the enol (II) of I, to produce, respectively, the intermediates III or V. A close analogy for this reaction is available (6). The proposed intermediate III, by mechanistic analogy with the behavior of N-benzyloxypyridinium bromide (2), should be convertible to either benzaldehyde or phenylglyoxylic acid (IV), or to both. These conversions have, in fact, been realized independently by isolating these two products from the reaction of α-bromophenylacetic acid and pyridine N-oxide, a reaction in which III must be an intermediate. It has also been shown that IV reacts with phenylacetic anhydride and pyridine to yield, by condensation, DPMA and, by decarboxylation, benzaldehyde (7). Finally, it has been demonstrated that acetylmandelic acid (V) undergoes a two-electron, decarboxylative oxidation under these reaction conditions to yield benzaldehyde.



I

II



$$\begin{tikzcd}
\underset{\text{III}}{C_6H_5\text{-}\overset{O\text{-}\overset{+}{N}C_5H_5}{CH}\text{-}COOH} \arrow[r, "-C_5H_5\overset{+}{N}H"] \arrow[dr, "-C_5H_5\overset{+}{N}H"', "-CO_2"] & \underset{\text{IV}}{C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}COOH} \arrow[r, "C_6H_5CH_2COOH", "Ac_2O"'] \arrow[d, "-CO_2"] & \text{DPMA} \\
\underset{\text{V}}{C_6H_5\text{-}\overset{OAc}{CH}\text{-}COOH} + C_5H_5NO \arrow[r, "Ac_2O"] & C_6H_5CHO + CO_2 + AcOH + C_5H_5N &
\end{tikzcd}$$

Further support for this mechanism has been obtained by the detection of the methyl esters of the proposed intermediates, IV (0.6-3%) and V (6.3-10.5%) in the esterified acid fractions of some of the product mixtures from the reaction of pyridine N-oxide with phenylacetic acid.

Further study of the synthetic and mechanistic implications of the several novel reactions reported here is now under way.

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References and Footnotes

1. An excellent analogy for this fragmentation is the acid catalyzed decomposition of certain diacylperoxides and peresters: P. D. Bartlett and J. E. Leffler, J. Am. Chem. Soc., 72, 5030 (1950); H. Hart and R. A. Cipriani, ibid., 84, 3697 (1962); C. Rüchardt and H. Swarzer, Angew. Chem., 74, 251 (1962).
2. W. Feely, W. L. Lehn and V. Boekelheide, J. Org. Chem., 22, 1135 (1957).
3. (a) The detection of 0.5% of this ester would have been possible. (b) However, this ester was detected by Rüchardt, Eichler and Krätz (4) under somewhat different reaction conditions. This presumably indicates that a carbonium ion fragmentation is not precluded under all conditions. (c) In a run in which the molar ratio of N-oxide to phenylacetic acid was 1.0 and in which a large excess of acetic acid and acetic anhydride was present, less than 0.15% of benzyl acetate (the reaction product of benzyl carbonium ions with acetic acid) was produced.
4. C. Rüchardt, S. Eichler and O. Krätz, Tetrahedron Letters, 4, 233 (1965)
5. (a) Small quantities (ca. 1%) of 2- and 4-benzylpyridine were, however, produced in this reaction. (b) See ref. 4 for other evidence against a radical reaction.
6. I. Lillien, J. Org. Chem., 29, 1631 (1964). However, several alternative paths for the production of III and V can also be envisioned.
7. The mechanistic implications of this novel decarboxylation will be discussed in a separate paper.